Mixed venous oxygen and carbon dioxide content

By Alex Yartsev - 25/07/2020
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This chapter is barely relevant to Section G4(vii) of the 2023 CICM Primary Syllabus which asks the exam candidate to *"describe the factors that affect venous oxygen saturation"*. Though the college were careful not to call it *central* venous oxygen saturation, it is safe to assume that this is what they were thinking, as peripheral venous oxygen saturation is basically useless. In contrast, central venous oxygen saturation can be useful, even though it has lost a lot of popularity since being run over by the ANZICS CTG party bus.

As always, a lack of clinical relevance does not deter the examiners from asking detailed questions about a subject, particularly where it is interesting from an abstract scientific standpoint. Even after being trampled in the literature, venous oxygenation has made frequent appearances in the CICM First Part exam. So far, it has been the subject of two SAQs:

- Question 13 from the second paper of 2021
- Question 19 from the first paper of 2017
- Question 10 from the first paper of 2008

Specifically, the stem of these questions asked for the mixed venous PO_2, the partial pressure of oxygen in mixed venous blood; the examiners' comments (*"...a number of candidates wrote about mixed venous oxygen saturation"* was listed among the common errors). Additionally, Question 23 from the second paper of 2015 and Question 7 from the first paper of 2011 asked about the determinants of mixed venous CO_2 content. As the concepts used to explain this are very similar, it was tagged on to the end of this chapter, for lack of a better place to put it.

In summary:

- **Mixed venous blood** is:
  - Blood sampled from the pulmonary artery which is mixed in the RV and which represents a weighted average of venous blood from all tissues and organs

- **Mixed venous saturation** is usually 70-75%, and is determined by:
  - **Mixed venous PO_2** which is usually 40 mmHg
  - **The p50 value** of the O_2-Hb dissociation curve in mixed venous blood, which is slightly right-shifted due to the Bohr effect
- **Mixed venous oxygen content** depends on:
  - **Total blood oxygen content = (SvO_2 × *ce*Hb × BO_2) + (PvO_2 × 0.03)**
    - **ceHb** = the effective haemoglobin concentration
    - **PvO_2** = the partial pressure of oxygen in mixed venous blood
    - **0.03** = the content, in ml/L/mmHg, of dissolved oxygen in blood
    - **BO_2 =** the maximum amount of Hb-bound O_2 per unit volume of blood (normally 1.39)
    - **SvO_2 =** oxygen saturation of mixed venous blood
  - **Balance of total body oxygen delivery and consumption,** expressed in terms of the modified Fick equation ($CO = VO_2 / CaO_2 - CvO_2$):
    - **Arterial oxygen content:** decreased arterial oxygenation will produce a decreased SvO_2
    - **VO_2,** the oxygen consumption rate: decreased VO_2 will produce an increased SvO_2
    - **Cardiac output:** a decreased cardiac output will produce a reduced SvO_2

This remains an attractive topic for review articles, albeit with a visible change in tone which has evolved over the years. From highly optimistic works published earlier this century (eg Emanuel Rivers et al, 2001), people are now publishing papers with titles like "*Should We Abandon Measuring SvO2 or ScvO2 in Patients with Sepsis?*"(Teboul et al, 2019). Pearse & Rhodes (2005) give a solid breakdown of the physiology (even including some normal values) and their work is refreshingly well-referenced. For mixed venous CO_2, there was no better overview than Lamia et al (2006), but Pearce & Rhodes (2005) also do this very well,

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Venous, central venous and mixed venous blood

It would seem logical to first establish what exactly we are talking about. In the briefest form possible,

- Venous blood is all blood flowing from the post-capillary venules back to the heart, after it has exchanged gas and other substances with the tissues.
- As a result of gas exchange, the composition of this blood will be different. There will be less oxygen in it, more CO_2, and other metabolic byproducts will be present.

- The difference in composition will therefore reflect metabolic activity. In short, there should be a relationship between cellular metabolism and venous blood composition, particularly its oxygenation (as oxygen consumption is a good representation of metabolic rate).

From, this, it follows logically that

- Oxygen content of blood taken from a vein will reflect the metabolic activity of the specific tissues from which the blood is draining.
- The oxygenation of venous blood in the central vessels should therefore be reflective of the metabolic activity of the entire body
- This information could be useful to guide therapy as it would allow a comparison between oxygen delivery and oxygen extraction (expressed as the oxygen extraction ratio)

It also follows that central venous oxygenation is much more important than the peripheral, and that if you want to assess the oxygen consumption of the entire organism, it is important to get as central as you can. As you will see below, even the 10cm difference between right atrial and pulmonary arterial sampling sites will matter by a few percentage points.

Acknowledging the fact that this chapter is drifiting into dangerously pragmatic territory, let us steer it back into abstract science and cynical test-savvy exam preparation.

Definition of mixed venous blood

Most SAQs on this topic have asked about mixed venous blood specifically, and the college comments appear to emphasise the definition of this term. From the perspective of incorporating the physiological importance of mixed venous blood into the definition, the most thorough attempt appears in Kandel & Aberman (1983):

> *"Mixed venous blood is ideally derived from a pool of venous blood with the following characteristics: (1) includes all the blood that has traversed capillary beds capable of extracting oxygen from blood; (2) excludes any blood that has not traversed capillary beds capable of extracting oxygen from the blood (eg, excludes blood shunted from the left ventricle to the right ventricle as in the*

> *presence of a ventricular septal defect); and (3) contains blood so thoroughly mixed that there is a single oxygen saturation throughout, despite being formed by blood with varying oxygen saturations."*

This definition only has one disadvantage, in that it has absolutely no respect for the reader's time or attention span. That might be fine in among the lettered subscribers of the *Archives of Internal Medicine,* but a CICM examiner who has already marked seventy questions will have no patience for circumlocution. Clearly, a defatted version is needed:

> *"Mixed venous blood is:*
>
> - *sampled from the pulmonary artery*
> - *mixed in the right ventricle out of multiple venous sources*
> - *representative of the oxygen extraction for the entire body"*

Or, from Part One, an even shorter definition which satisfies all the essential criteria from the examiner's comments:

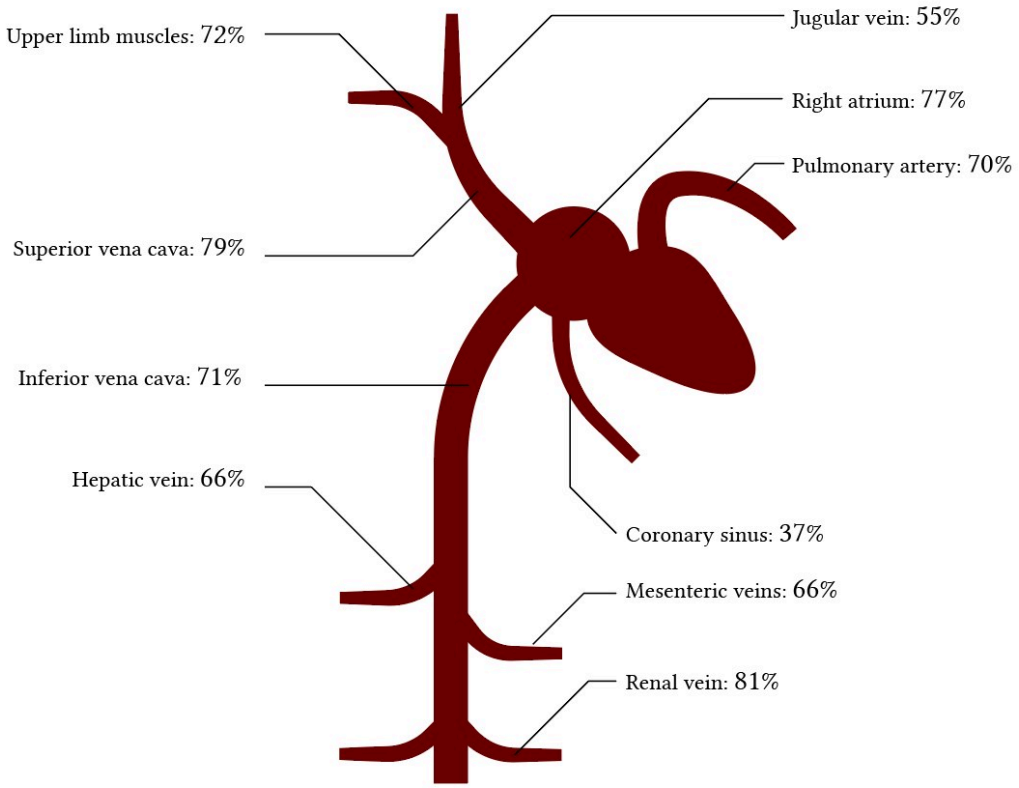
> *"Blood from the IVC, SVC and coronary sinus, which has been mixed by the pumping action of the RV and is typically sampled from the pulmonary artery"*

Or, one which contains the absolute minimum of information while remaining borderline accurate:

> *"Mixed venous blood is pulmonary arterial blood."*

Composition of *mixed* venous blood

"Good answers also provided the varying PO_2 from different tissue beds that make up mixed venous blood", commanded the examiners in their SAQ commentary. One might point out that, by definition, *all* tissue beds make mixed venous blood. Some representative contributors from this large pool are included as labelled elements of the following diagram:



This is actually a modification of a well-known diagram by Konrad Reinhart, traceable back to his mellifluously titled *"Zum Monitoring des Sauerstofftransportsystems"*(1988). Not only is it in German, but it is also impossible to get a hold of an electronic copy of *Der Anaesthesist* from 1988. Thus, we may never know where those numbers came from. Moreover, not all of the numbers seem plausible, and some were missing. The SVC and IVC values had to be pulled from Leiner et al (2008), renal vein from Nielsen et al (1992), and jugular from Nakamura (2011).

Difference between SvO_2 and $ScvO_2$

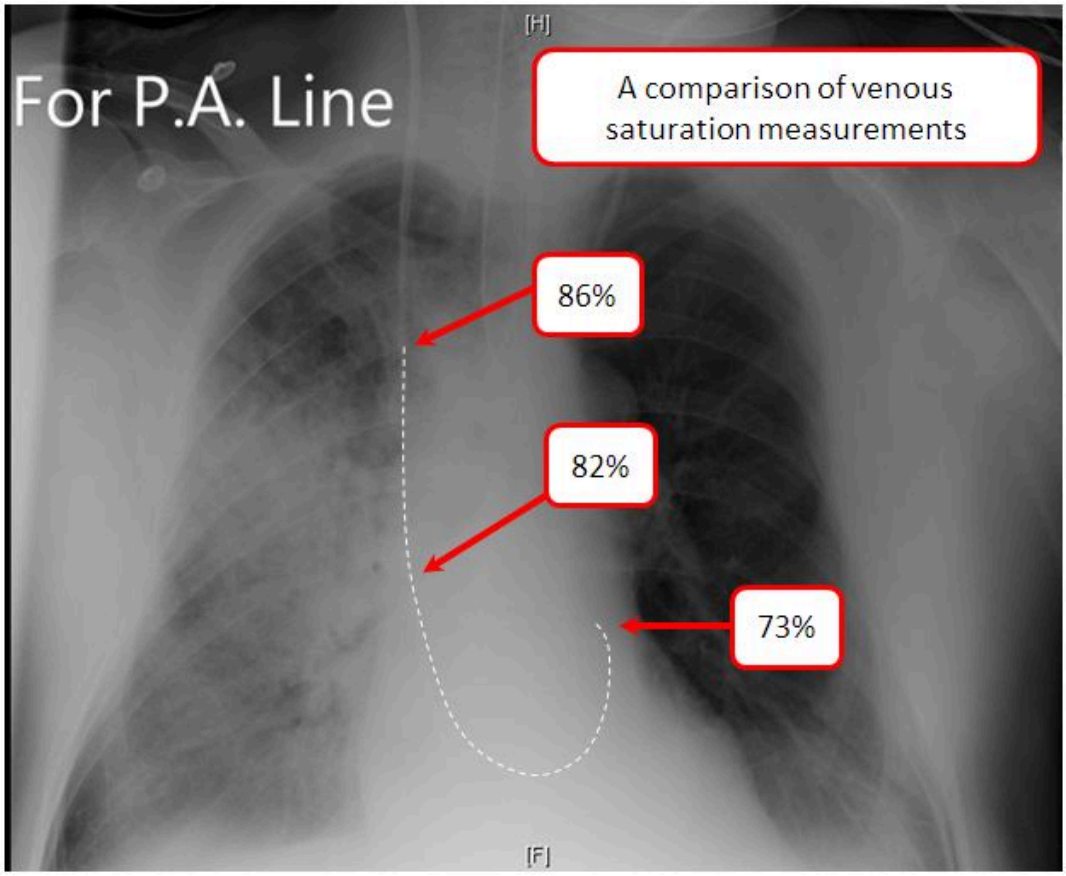
There is broad agreement in the literature that there is a difference central venous oxygen saturation (ScvO2) and mixed venous oxygen saturation (SvO2), even though not everybody agrees that the difference is clinically significant.

There occasionally seems to be some disagreement as to which is higher. Oh's Manual (p.154 of the 7th ed). specifies that under normal physiological conditions central venous saturation ($ScvO_2$) is 2-3% lower than mixed venous oxygen saturation (SvO_2). So, if one's cross-table viva examiner happens to be Thomas

John Morgan or Balasubramanian Venkatesh, one would be wise to regurgitate this information.

Fortunately, they probably do not participate in First Part vivas; as their chapter is pretty much the only resource which makes this claim. Average values measured directly in healthy volunteers by Barrat-Boyes et al (1957) got an average of 78.4% in the SVC and 76.8% in the pulmonary artery. The drop in oxygen content between central venous and pulmonary arterial blood is usually attributed to the blood coming out of the venous sinus, which is typically quite anoxic (the heart being an organ with a famously high oxygen extraction ratio).

Most other resources give an even lower normal value for the SvO_2, perhaps because they are referring to critically ill patients with high myocardial oxygen demand. A 2004 study published in Chest would have us believe that the $ScvO_2$ is 5% higher than the SvO_2, and implies that the difference may be a measure of increased myocardial oxygen consumption. Yet another review article reports that this difference changes with the CVC sampling tip position (at 15cm from the tricuspid valve, the $ScvO_2$ was 8% higher, but in the right atrium it was only 1% higher). Certainly older papers felt that right atrial blood was mixed well enough for experimental work in healthy subjects (eg. Hamilton et al, 1948). Perhaps, the more severe the shock the greater the difference. The following image illustrates the venous oxygen saturation values at three different sites along the PA catheter (sheath, proximal injector port, distal PA port) of a sedated ventilated patient with severe septic shock and a markedly hyperdynamic circulation:



Venous oxygen saturation (SvO_2), partial pressure and content

The majority of textbooks give a partial pressure (PvO_2) of around 40mmHg, which corresponds to a mixed venous oxygen saturation value of around 70-75% (Barrat-Boyes et al, 1957). When it comes to making some sort of practical use out of venous blood gas results, the PvO_2 is generally held to be a minor player, as it contributes minimally to the calculation of mixed venous oxygen *content*. And it is the content you need, if you were going to be calculating something useful.

The oxygen *content* of mixed venous blood has many influences, which are basically the same as all the normal things that influence the oxygen content of whole blood. These are:

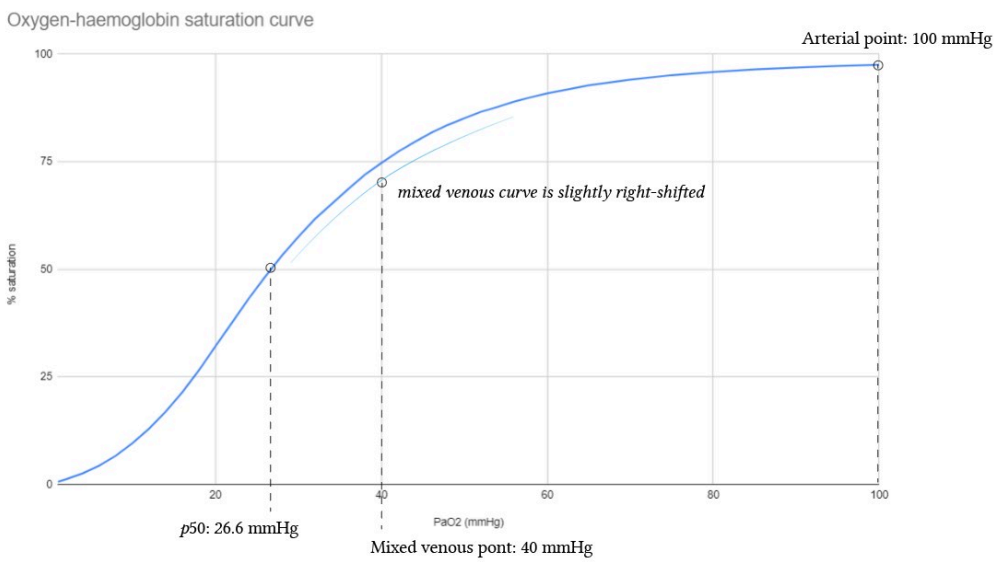
Total blood oxygen content = $(sO_2 \times ceHb \times BO_2) + (PO_2 \times 0.03)$

Where:

- ceHb = the effective haemoglobin concentration

- PO_2 = the partial pressure of oxygen in the blood
- 0.03 = the content, in ml/L/mmHg, of dissolved oxygen in blood
- BO_2 = the maximum amount of Hb-bound O_2 per unit volume of blood (normally 1.34 or 1.39)
- sO_2 = oxygen saturation

These determinants are not special, in the sense that there is nothing especially venous about them that can't also be said about arterial blood. Thus, if one were to discuss these in an exam answer about mixed venous oxygen saturation, one would probably have to bring in some additional elements. A good one would be the difference in oxygen-carrying capacity between the arterial and venous blood which is brought about by a shift in the oxygen-haemoglobin dissociation curve:



Because mixed venous blood contains more dissolved CO_2, and is more acidic, the p50 value shifts right (this is the Bohr effect). The magnitude of the shift under normal circumstances is probably not very great. Those few authors who actually report mixed venous p50 values from normal subjects (eg. Kronenberg et al, 1971) tend to report values within a range the borders of which include normal arterial p50 (26.6 mmHg).

However, let us come back to the college SAQs, which specifically asked for the mixed venous PO_2, and actually penalised people who tried to steer the question into more meaningful territory. How do we distill the complex interplay of abovementioned factors into a form which puts this relatively minor parameter front and centre? You could probably say something like this:

- The PO_2 in mixed venous blood is a major determinant of its oxygen content:

- The PO_2 describes the proportion of dissolved oxygen ($PO_2 \times 0.03$)
- The PO_2 also determines the SvO_2 according to the shape of the oxygen-haemoglobin dissociation curve in mixed venous blood
    - This curve is slightly right-shifted (compared to arterial blood) because of the Bohr effect
- The SvO_2 then determines the oxygen carriage by haemoglobin in mixed venous blood, and therefore the mixed venous oxygen content

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Determinants of mixed venous oxygen content

Apart from the determinants of oxygen-carrying capacity, the oxygen content of mixed venous blood is determined by the following main factors:

- How much oxygen there was in it before it became venous blood; i.e. **arterial oxygen content**
- How much of this arterial blood was delivered to the tissues, i.e. the **cardiac output,**
- How much oxygen was extracted from it by the tissues, i.e. the **systemic oxygen consumption (VO_2)**

These determinants, if you look closely, are the components of the Fick equation, where the cardiac output is calculated from the ratio of systemic oxygen consumption to the arteriovenous difference in oxygen content:

$$CO = \frac{VO_2}{CaO_2 - CvO_2}$$

where

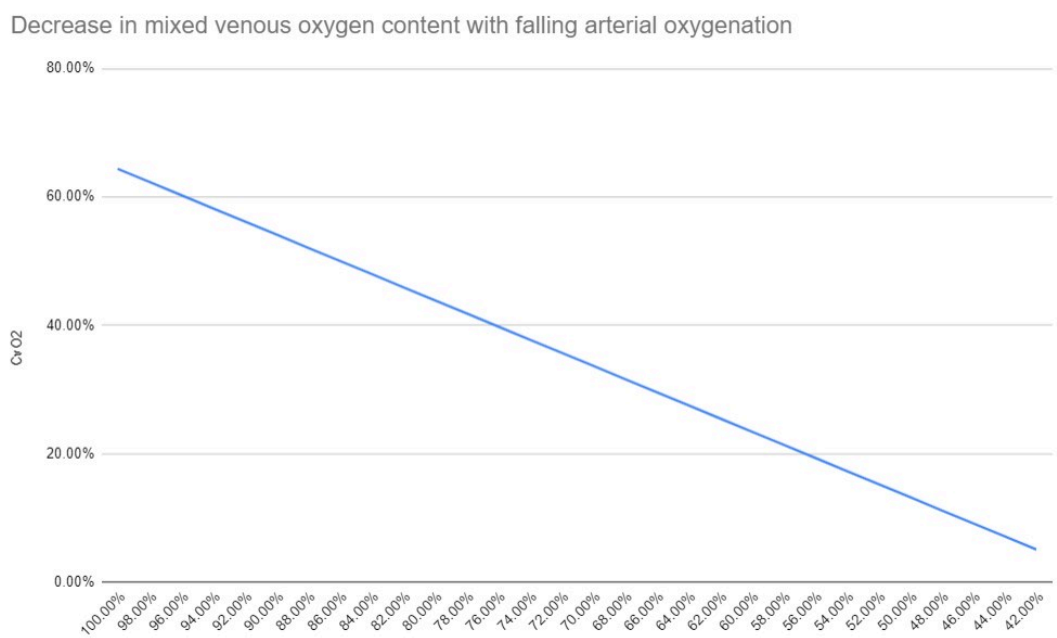
- CO is the cardiac output,
- VO_2 is the oxygen consumption of the organism, in ml/min,
- CaO_2 is the arterial oxygen content in ml/L, and
- CvO_2 is the venous oxygen content.

Rearranged to solve for CvO_2, we get this:

$$CvO_2 = CaO_2 - \frac{VO_2}{CO}$$

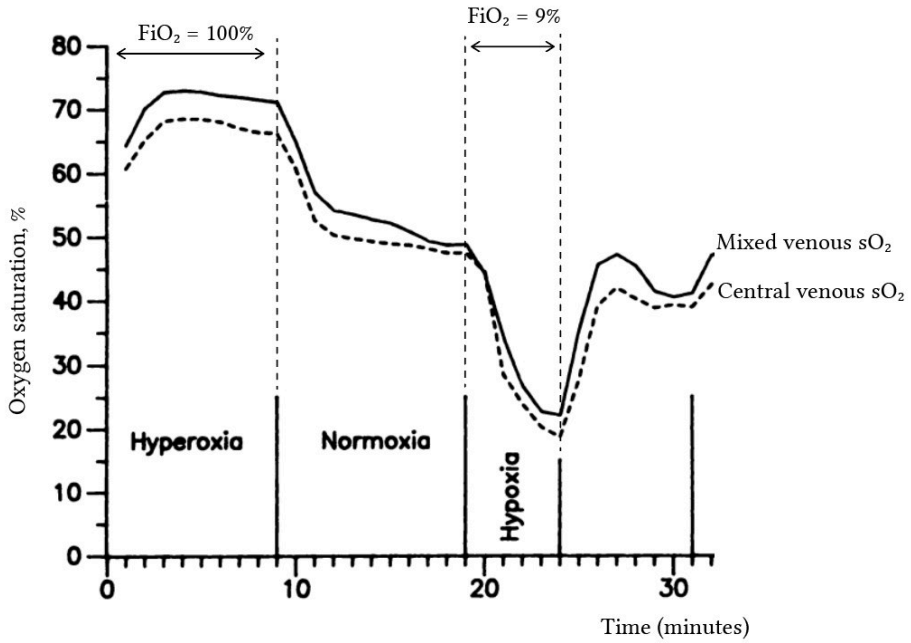
Mixed venous oxygen content and arterial oxygenation

If one needed to describe the importance of arterial oxygenation on mixed venous oxygenation, one could probably produce a crude graph (usung the abovementioned equation) where the oxygen consumption (VO_2) stays the same while the CaO_2 drops:



It would probably have been easier to just say that the mixed venous oxygenation drops in proportion to the fall in arterial oxygenation, all other things remaining equal. They usually do not remain equal, of course (consider that the cardiac output and pH would not remain calmly unchanged as the SaO_2 decreases to 50%). The oxygen demand of the tissues generally remains the same, however, and if you deliver less oxygen to them, then less oxygen will be left over in the venous blood after they are done with it. The same is true for an increase in

oxygen supply. Here, a graph from Reinhart et al (1989) demonstrates the effects of hypoxia and hyperoxia on the SvO2 and ScvO2 of some experimental animals:



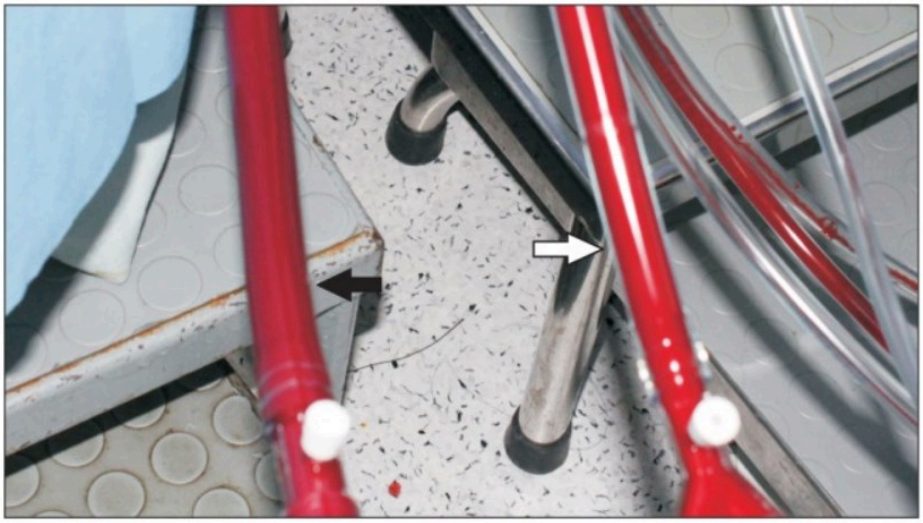
Mixed venous oxygen content and VO_2

VO_2, the rate of tissue oxygen consumption, is obviously going to determine how much oxygen is left in the arterial blood as it passed through the tissues and becomes venous. This concept, along with the oxygen extraction ratio, is discussed in greater detail in the chapter on the relationship between venous oxygenation and cellular metabolism. In brief, if the cardiac output and arterial oxygen remain the same, then an increase in systemic oxygen consumption will produce a decrease in mixed venous oxygen content, as more oxygen is being extracted. Similarly, anything that decreases the total body oxygen consumption will lead to an increase in SvO_2.

Manoeuvres which reduce the total body metabolic demand clearly do increase the mixed venous oxygen content. For example, the induction of anaesthesia with sufentanil and suxamethonium increased the SvO_2 from 75% to 82% on average, while the cardiac output decreased slightly (Colonna-Romano et al, 1994). Going further, in already anaesthetised patients undergoing cardiac surgery, Hu et al (2016) found the SvO_2 increased from 79% to 83% when the patients were cooled to about 30°C. As more cooling is performed, the total body metabolic rate

decreases even further. Pesonen et al (1999) recorded an SvO_2 of 93% in children at 21°C, just before the commencement of deep hypothermic circulatory arrest.

Hypothetically, if the body was using *absolutely no oxygen*, the mixed venous oxygen content would be identical to the arterial ($CaO_2 = CvO_2$). This is why cyanide toxicity is something of a classic of SvO_2 literature, as cyanide has the effect of completely abolishing mitochondrial oxygen metabolism, effectively preventing the tissues from using any of the circulating oxygen. Martin-Bermudez et al (1997) report a case of intentional cyanide ingestion where the SvO_2 increased to 95.2%, something the literature tends to describe as *arteriolization*. The most extreme example comes from Chung et al (2016), reporting on their management of a 77 year old woman who ended up with an SvO_2 of 99.8% in a case of nitroprusside toxicity while on bypass. The original image from their paper is reproduced here as a quite salute to the Korean anaesthetist who pulled out his phone and took a shot of the lines while theatre staff were frantically diluting the thiosulfate.



Bright red-colored blood is observed at the venous line of the cardiopulmonary bypass (black arrow) which is similar to that of the arterial line (white arrow).

Mixed venous oxygen content and cardiac output

Lastly, cardiac output influences the mixed venous oxygen concentration, to the point where the SvO_2 has been suggested as a surrogate measure of cardiac output. This is discussed at length in the chapter on the practical use of central and mixed venous blood gases.

If the cardiac output decreases, the venous oxygen content will also decrease, provided everything else remains the same. The oxygen content of arterial blood is only worth something if that blood is being pumped around. If the circulation is slow and sluggish, the rate of oxygen delivery to the tissues ends up being relatively slow, while the rate of oxygen extraction remains the same - which naturally gives rise to a decrease in the mixed venous oxygen content. Similarly, if the rate of oxygen delivery increases well above the level of tissue demand, the leftover blood in the venous circulation will still be reasonably well oxygenated. From this, one might come to the conclusion that measuring the SvO_2 might be a reasonably good method of estimating the cardiac output (or at least detecting changes in it), but unfortunately in the real world of the patient's bedside this is not the case.

Mixed venous CO_2 content

Having seen the main determinants of mixed venous oxygen content, the reader will by now have realised that it is easy to apply the exact same principles to mixed venous CO_2. Observe:

- **Mixed venous PCO_2** is usually about 46 mmHg, and is determined by the total oxygen content of mixed venous blood and the shape of the CO_2 dissociation curve
- **The total CO_2 content of mixed venous blood,** which is usually about 520 ml/L, is described by the modified Fick equation:

  $$VCO_2 = CO \times k \times (PvCO_2 - PaCO_2)$$

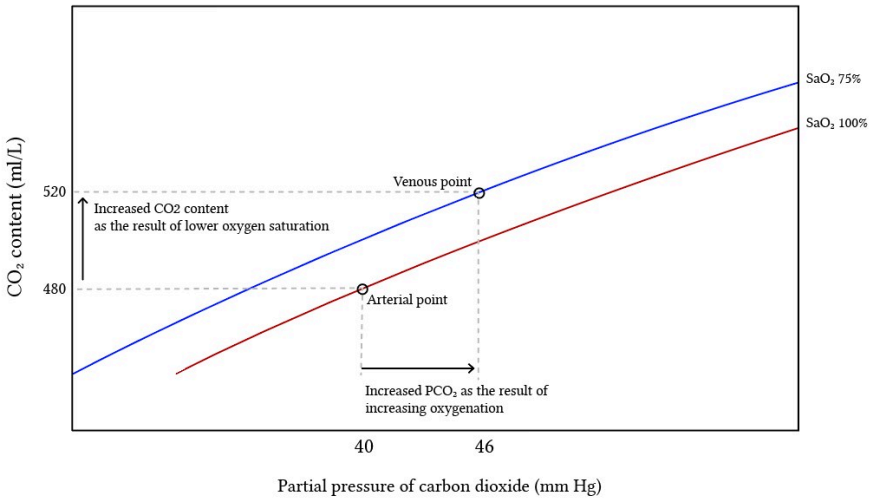
  where

  - VCO_2 is the rate of CO_2 production,
  - CO is the cardiac output,
  - $PvCO_2 - PaCO_2$ is the arteriovenous CO_2 difference, and
  - k is a coefficient used to describe the near-linear relationship between CO_2 content and partial pressure in the blood.

  - **The CO_2 content of arterial blood** - any increase in arterial CO_2 will be inherited by the mixed venous CO_2. This is controlled by the central ventilation reflexes.

- **CO_2 production in the tissues,** which is related to the rate of aerobic metabolism and oxygen consumption (VO_2). A low metabolic rate will cause a decrease in mixed venous CO_2 (eg. hypothermia).
- **Cardiac output,** which determines the rate of tissue CO_2 removal.
  - Poor cardiac output (eg. in cardiogenic shock) will cause an increased mixed venous CO_2 by a "stagnation phenomenon"
    - I.e. an abnormally large amount of CO_2 will be added to capillary blood per unit volume if the transit time is increased (i.e. flow is decreased)

- **The CO_2-carrying capacity of blood,** which is described by the CO_2 dissociation curve:



  - The curve is left-shifted because deoxygenated haemoglobin has a higher affinity for CO_2 (the Haldane effect).

Previous chapter: Physiological factors which contribute to central venous pressure

Next chapter: The relationship of venous oxygenation and cellular metabolism

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